DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

March 26, 2009

Todd W. Rich, M.D.
V.P. Development Regulatory Affairs
Genentech Inc.
1 DNA Way
South San Francisco, CA 94080-4990

RE: BLA No. 125085 Avastin® (Bevacizumab)
BLA No. 125156 LUCENTIS™ (ranibizumab injection)
BLA No. 103705, 103737 RITUXAN® (rituximab)
BLA No. 103976 Xolair® (Omalizumab) For Subcutaneous Use
BLA No. 103792 HERCEPTIN® (trastuzumab)
BLA No. 103532 Pulmozyme® (dornase alfa) Inhalation Solution
MACMIS ID #17309

Dear Dr. Rich:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed Genentech Incorporated's (Genentech) sponsored links on internet search engines (e.g., Google.com) for the following products: Avastin® (Bevacizumab) (Avastin), LUCENTIS™ (ranibizumab injection) (Lucentis), RITUXAN® (rituximab) (Rituxan), Xolair® (Omalizumab) (Xolair), HERCEPTIN® (trastuzumab) (Herceptin), and Pulmozyme® (dornase alfa) (Pulmozyme). The sponsored links cited in this letter are misleading because they make representations and/or suggestions about the efficacy of Avastin, Lucentis, Rituxan, Xolair, Herceptin, and Pulmozyme, but fail to communicate **any** risk information associated with the use of these drugs. In addition, the sponsored links for Avastin, Lucentis, Rituxan, Xolair, and Herceptin inadequately communicate the drugs' indications. Furthermore, the sponsored links for Avastin, Lucentis, Xolair, and Pulmozyme fail to use the required established name. Thus, the sponsored links misbrand the drugs in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. *See* 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 201.10(g)(1), 202.1(b)(1), (e)(3)(i), (ii) & (e)(6)(i).

Background

Avastin

According to its FDA-approved product labeling (PI), Avastin is indicated, among other things, in combination with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.

Avastin is associated with a number of risks, as reflected in the Boxed Warning, Warnings, Precautions, and Adverse Reactions sections of its PI.

Lucentis
According to its FDA-approved PI, Lucentis is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration.

Lucentis is associated with a number of risks, as reflected in the Contraindications, Warnings and Precautions, and Adverse Reactions sections of its PI.

Rituxan
According to its FDA-approved PI, Rituxan is indicated for the treatment of non-Hodgkin's Lymphoma (NHL) patients with:

- Relapsed or refractory, low-grade or follicular, CD-20-positive, B-cell, NHL as a single agent
- Previously untreated follicular, CD-20-positive, B-cell NHL in combination with CVP chemotherapy
- Non-progressing (including stable disease), low-grade, CD-20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive, NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.

Rituxan in combination with methotrexate is also indicated to reduce signs and symptoms and to slow the progression of structural damage in adult patients with moderately-to-severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

Rituxan is associated with a number of risks, as reflected in the Boxed Warning, Warnings and Precautions, and Adverse Reactions sections of its PI.

Xolair
According to its FDA-approved PI, Xolair is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

Xolair is associated with a number of risks, as reflected in the Boxed Warning, Contraindications, Warnings, Precautions, and Adverse Reactions sections of its PI.

Herceptin
According to its FDA-approved PI, Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- with docetaxel and carboplatin

- as a single agent following multi-modality anthracycline based therapy.

Herceptin is also indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Herceptin is associated with a number of risks, as reflected in the Boxed Warning, Warnings and Precautions, and Adverse Reactions sections of its PI.

Pulmozyme

According to the Indications and Usage section of its FDA-approved PI,

> Daily administration of Pulmozyme® (dornase alpha) Inhalation Solution in conjunction with standard therapies is indicated in the management of cystic fibrosis patients to improve pulmonary function. In patients with an FVC ≥ 40% of predicted, daily administration of Pulmozyme has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics.

The Indications and Usage section of the PI also includes the important limitation that the safety and efficacy of daily administration have not been demonstrated in patients for longer than 12 months.

Pulmozyme is associated with a number of risks, as reflected in the Contraindications, Precautions, and Adverse Reactions sections of its PI.

Omission of Risk Information

Promotional materials, other than reminder pieces, which include the name of the drug product but do not include indications or other representations or suggestions relative to the drug product (see 21 CFR 200.200, 201.100(f), 202.1(e)(2)(i)), are required to disclose risk and other information about the drug. Such materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The sponsored links present the following claims:

- Rectal Cancer Treatment
  Learn about Avastin® treatment from Genentech. Visit the official site.
  www.Avastin.com

- Lucentis® Improves Vision
  www.Lucentis.com Studies Show 95% of Patients Maintained Vision and 40% Improved.

- Rituxan ® (Rituximab)
  Rituxan ® is FDA-approved to treat non-Hodgkin's lymphoma and RA.
  www.Rituxan.com

- Allergic Asthma Info
  www.Xolair.com Are you suffering from allergic asthma? The cause might be IgE.

- Herceptin ® (trastuzumab)
  www.Herceptin.com Treating patients with breast cancer since 1998. Official site.

- Cystic Fibrosis Treatment
  www.Pulmozyme.com
  FDA-approved Pulmozyme® medication for Cystic Fibrosis.

These sponsored links make representations and/or suggestions about the efficacy of Avastin, Lucentis, Rituxan, Xolair, Herceptin, and Pulmozyme, respectively, but fail to communicate **any** risk information. This omission of risk information is particularly concerning as four of the products, Avastin, Rituxan, Xolair, and Herceptin, have Boxed Warnings. For promotional materials to be truthful and non-misleading, they must contain risk information in each part as necessary to qualify any claims made about the drug.

By omitting the most serious and frequently occurring risks associated with the drugs promoted in the links above, the sponsored links misleadingly suggest that Avastin, Lucentis, Rituxan, Xolair, Herceptin, and Pulmozyme are safer than has been demonstrated. We note that these sponsored links contain a link to the products' websites. However, this is insufficient to mitigate the misleading omission of risk information from these promotional materials.

Inadequate Communication of Indication

The sponsored links for Avastin, Lucentis, Rituxan, Xolair, and Herceptin provide very brief statements about what the drugs are for; however, these statements are incomplete and misleading, suggesting that these drugs are useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

Specifically, the sponsored link for Avastin misleadingly broadens the indication for Avastin by implying that any patient with rectal cancer is a candidate for Avastin therapy ("Rectal Cancer Treatment. Learn about Avastin® treatment from Genentech…."), when this is not the case. Rather, Avastin is indicated for patients with metastatic carcinoma of the rectum. The link also fails to reveal other material information about the indication of the drug, including that it is only indicated in combination with intravenous 5-fluorouracil-based chemotherapy for patients with metastatic rectal cancer.

The sponsored link for Lucentis misleadingly broadens the indication for Lucentis by implying that all patients with vision problems are candidates for Lucentis therapy ("Lucentis®

Improves Vision"), when this is not the case. Rather, Lucentis is only indicated in patients with neovascular (wet) age-related macular degeneration.

Similarly, the sponsored link for Rituxan misleadingly broadens the indication for Rituxan by implying that any patient with non-Hodgkin's lymphoma (NHL) or rheumatoid arthritis (RA) is a candidate for Rituxan therapy ("Rituxan® is FDA-approved to treat non-Hodgkin's lymphoma and RA"), when this is not the case. Rather, Rituxan's indications are limited to specific categories of NHL and RA patients, as described in the Background section above. The link also fails to reveal other material information about the indications of the drug, including that it is only indicated as part of a combination regimen for certain non-Hodgkin's lymphoma patients, and that it is not indicated for first-line or monotherapy use for rheumatoid arthritis.

The sponsored link for Xolair misleadingly broadens the indication for Xolair by implying that all patients with allergic asthma are candidates for Xolair therapy ("Are you suffering from allergic asthma? The cause might be IgE"; presented along with the name of the drug), when this is not the case. Rather, as stated in its PI, Xolair is only indicated for patients 12 years and older with moderate to severe persistent asthma "who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids." Additionally, the sponsored link fails to convey that the safety and efficacy of Xolair has not been established in other allergic conditions.

The sponsored link for Herceptin misleadingly broadens the indication for Herceptin by implying that the drug is approved to treat any type of breast cancer ("….Treating patients with breast cancer since 1998"), when this is not the case. Rather, Herceptin is indicated for the treatment of **HER2 adjuvant and metastatic** breast cancer as either part of a treatment regimen or as a single agent in particular circumstances.

Failure to Use Required Established Name

The sponsored links for Avastin, Lucentis, Xolair, and Pulmozyme fail to present the full established name of the drugs being promoted, despite the requirement to do so. *See* 21 CFR 201.10(g)(1) & 202.1(b)(1).

Conclusions and Requested Action

For the reasons discussed above, the sponsored links misbrand Avastin, Lucentis, Rituxan, Xolair, Herceptin, and Pulmozyme, in violation of the Act and FDA regulations. *See* 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 201.10(g)(1), 202.1(b)(1), (e)(3)(i), (ii) & (e)(6)(i).

DDMAC requests that Genentech immediately cease the dissemination of violative promotional materials for Avastin, Lucentis, Rituxan, Xolair, Herceptin, and Pulmozyme, such as those described above. Please submit a written response to this letter on or before April 9, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for these drugs as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such materials. Finally, we encourage you to

review your promotional materials for the other prescription drug products that Genentech promotes in the United States and to discontinue or revise any materials with the same or similar violations, and request that your response address this issue as well.
Please direct your response to the undersigned at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 17309 in addition to the BLA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Avastin, Lucentis, Rituxan, Xolair, Herceptin, and Pulmozyme comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

/s/

Shefali Doshi, M.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications